The Milieu of Damaged AEC2 Stimulates Alveolar Wound Repair by Endogenous and Exogenous Progenitors.

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Public Summary:
Alveolar epithelial integrity is dependent upon the alveolar milieu, yet the milieu of the damaged alveolar epithelial cell type 2 (AEC2) has been little studied. Characterization of its components may offer the potential for ex vivo manipulation of stem cells to optimize their therapeutic potential. We examined the cytokine profile of AEC2 damage milieu, hypothesizing that it would promote endogenous epithelial repair while recruiting cells from other locations and instructing their engraftment and differentiation. Bronchoalveolar lavage and lung extract from hyperoxic rats represented AEC2 in vivo damage milieu, and medium from a scratch-damaged AEC2 monolayer represented in vitro damage. CINC-2 and ICAM, the major cytokines detected by proteomic cytokine array in AEC2 damage milieu, were chemoattractive to normoxic AECs and expedited in vitro wound healing, which was blocked by their respective neutralizing antibodies. The AEC2 damage milieu was also chemotactic for exogenous uncommitted human amniotic fluid stem cells (hAFSCs), increasing migration greater than 20-fold. hAFSCs attached within an in vitro AEC2 wound and expedited wound repair by contributing cytokines migration inhibitory factor and plasminogen activator inhibitor 1 to the AEC2 damage milieu, which promoted wound healing. The AEC2 damage milieu also promoted differentiation of a subpopulation of hAFSCs to express SPC, TTF-1, and ABCA3, phenotypic markers of distal alveolar epithelium. Thus, the microenvironment created by AEC2 damage not only promotes autocrine repair but also can attract uncommitted stem cells, which further augment healing through cytokine secretion and differentiation.

Scientific Abstract:
Alveolar epithelial integrity is dependent upon the alveolar milieu, yet the milieu of the damaged AEC2 has been little studied. Characterization of its components may offer the potential for ex vivo manipulation of stem cells to optimize their therapeutic potential. We examined the cytokine profile of AEC2 damage milieu, hypothesizing that it would promote endogenous epithelial repair whilst also recruiting cells from other locations and instructing their engraftment and differentiation. BAL and lung extract from hyperoxic rats represented AEC2 in vivo damage milieu, while medium from a scratch-damaged AEC2 monolayer represented in vitro damage. CINC-2 and ICAM, the major cytokines detected by proteomic cytokine array in AEC2 damage milieu, were chemo-attractive to normoxic AEC, and expedited in vitro wound healing, which was blocked by their respective neutralizing antibodies. The AEC2 damage milieu was also chemotactic for exogenous uncommitted human amniotic fluid stem cells (hAFSCs), increasing migration >20 fold. HAFSC attached within an in vitro AEC2 wound, and expedited wound repair by contributing cytokines MIF and PAI-1 to the AEC2 damage milieu, which promoted wound healing. The AEC2 damage milieu also promoted differentiation of a sub-population of hAFSC to express SPC, TTF-1 and ABCA3, phenotypic markers of distal alveolar epithelium. Thus the microenvironment created by AEC2 damage not only promotes autocrine repair, but also can attract uncommitted stem cells which further augment healing through cytokine secretion and differentiation.